

EXHIBIT 24

SUPPLEMENTAL EXPERT REPORT OF DR. MICHAELA ALMGREN

1. The attorneys who represent death-sentenced prisoner Terry Lynn King asked me to submit an expert medical and scientific opinion in this case. I offered an initial expert report on November 17, 2021. I am now supplementing the opinions that I offered in that initial report based on my review of additional pharmacy related documents (Defts. Supp. Resp. 11.18.2021 000001-38).

2. My experience, qualifications, testimony in prior cases, and fee schedule for this case are set forth in my initial report.

3. More documents, studies, and other pertinent information may become available to me at a later date, and I reserve the right to take such materials into account and to modify or supplement my opinions accordingly. I may also be present at hearings or at trial and may consider any testimony or other evidence related to my opinions and modify/supplement my opinions accordingly

I. Quality concerns about the Active Pharmaceutical Ingredients used in preparation of Lethal Injection Chemicals.

4. Active pharmaceutical ingredients (APIs) are typically ordered from bulk suppliers, some of which manufacture the API while others are repackers who take the bulk API from the original manufacturer and repackage it, most commonly into a different size container. It is important to verify the quality of the API prior to compounding, as contamination may occur if the API has been repackaged. This can be done by performing qualitative testing as specified by the monograph for the API. There have been a number of FDA alerts and recalls issued due to adulteration and misbranding of APIs, even from well-known sources such as the Professional Compounding Centers of America.

5. As APIs can be purchased from different sources, it is crucial to assure that the quality of the API is tested for compliance with U.S. Pharmacopeia ("USP"). USP provides quality standards for medications, such as midazolam, as well as other medications and

excipients. A monograph for each USP grade medication will articulate quality requirements and specific test methods to be used to verify whether each quality measure is met. Only if a medication meets all quality standards as described by USP is it labelled as USP grade. Other possible chemical grades include ACS grade, which refers to American Chemical Society quality grade and follows ACS quality standards; EP grade, which means that the medication complies with quality requirements for European Pharmacopoeia; BP grade defines quality standards under British Pharmacopoeia; laboratory grade is another common classification but should not be used for medications, as it is not sufficiently pure. To compound medications according to USP requirements, USP grade quality standards must be followed for the drug to be labelled and used as USP grade. These different pharmacopeial standards are not harmonized and often set different quality requirements for the same medication. Also, testing methodology often differs. Different types of equipment and testing methodology are commonly used, which means that the results are not comparable when looking at the reported values. Thus, it cannot be assumed that because API has passed EP or BP quality standards that it is also in compliance with USP quality requirements. Just because purity or assay for a drug is reported as 99% according to one pharmacopeia does not mean that this number would be acceptable by the standards of another pharmacopeia due to differences in pharmacopeia analytical procedures.

6. From the supplemental documentation provided, midazolam API that has a manufacturing date of 11/01/2018 was not tested under the USP quality standards, but under the EP quality requirements. (Defts. Supp. Resp. 11.18.2021 000003). This means that the quality attributes examined were different than those required by USP. According to USP, the quality standards listed as per USP monograph for midazolam are:

- a. Identification (Spectroscopic ID via IR), Pass,
- b. Assay HPLC analysis specified in the monograph, 98.5%-101.5% on dried basis,

c. Loss on Drying, NMT 0.5% loss

d. Inorganic impurities via residue on ignition method, NMT 0.1%,

7. The current version of USP monograph for midazolam specifies the following acceptance criteria for organic impurities tested via HPLC method:

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Reduced midazolam ^a	0.20	1.0	0.1
Reduced reduced midazolam ^b	0.24	1.0	0.1
Amino compound ^c	0.25	0.5	0.1
Oxide midazolam ^d	0.46	1.3	0.1
Nitromethylene compound ^e	0.76	1.0	0.1
Dihydromidazolam ^f	0.83	0.5	0.1
Midazolam	1.0	—	—
Desfluoromidazolam ^g	1.14	1.0	0.2
6 <i>H</i> -isomer ^h	2.48	0.7	0.1
Unknown impurity	—	1.0	0.1
Total impurities	—	—	0.5

^a 8-Chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

^b 8-Chloro-6-(2-fluorophenyl)-3a,4,5,6-tetrahydro-1-methyl-3*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

8. EP Quality requirements for Midazolam are:

a. Identification using EP Method 2.2.24 Identification B (this method utilizes GC chromatography, not HPLC and IR as specified in USP monograph)

b. Appearance of Solution (not required per USP Monograph)

c. Related Substances EP method 2.2.29 via HPLC assay

<= 0.2% Impurity B

<= 0.15% each of impurity A, E, G, H

<= 0.10% unspecified impurities

<= 0.3% total impurities

- d. Impurity C EP method 2.2.27 via thin layer chromatography (not used in USP Monograph)
- e. Loss on Drying EP method 2.2.32 $\leq 0.5\%$ (similar to USP)
- f. Sulfated Ash EP method 2.4.14 $\leq 0.1\%$ (not USP required)
- g. Residual Solvents: meets requirements
- h. Solubility: insoluble in water, freely soluble in acetone, ethanol and methanol (not required per USP)

9. Here is the EP quality certificate for the midazolam with a manufacturing date of 11/01/2018:

MIDAZOLAM, EP*		
Batch/Lot Number :		
Manufacturing Date :	11/01/2018	
Expiration Date :	10/31/2023	
Retest Date :	NOT APPLICABLE	
CAS:		* All dates in this document are in format mm/dd/yyyy unless otherwise specified
TESTS	SPECIFICATIONS	RESULTS
ASSAY ON DRIED SUBSTANCE	98.5 - 101.5 %	99.9 %
DESCRIPTION	White or yellowish crystalline powder.	CONFORMS
IDENTIFICATION B (2.2.24)	IR: Reference to standard spectrum	POSITIVE
APPEARANCE OF SOLUTION	The solution is clear (2.2.1) and not more intensely coloured than the reference solution Y6. (2.2.2.11).	CONFORMS
RELATED SUBSTANCES (2.2.29)	$\leq 0.2\%$ (Impurity B)	NOT DETECTED
	$\leq 0.15\%$ (Each impurity A, E, G, H)	$< 0.15\%$
	$\leq 0.10\%$ (Unspecified impurities)	NOT DETECTED
	$\leq 0.3\%$ (Total impurities)	$< 0.3\%$
IMPURITY C (2.2.27)	$\leq 0.1\%$	$< 0.1\%$
LOSS ON DRYING (2.2.32)	$\leq 0.5\%$	0.01 %
SULFATED ASH (2.4.14)	$\leq 0.1\%$	0.04 %
RESIDUAL SOLVENTS	Meets the requirements.	CONFORMS
SOLUBILITY	Practically insoluble in water, freely soluble in acetone and in ethanol (96%), soluble in methanol.	
PACKAGING AND STORAGE	Preserve in tight, light-resistant containers.	

(Defts. Supp. Resp. 11.18.2021 000003).

10. It is apparent that the quality standards as set by USP monograph are different from EP monograph for midazolam. Completely different analytical methodology is used for identification procedure, and the impurities are not identified in the EP methodology as they are

in the USP method. It cannot be verified that the drug meets this requirement so it is not possible to verify that the quality of the midazolam API meets USP requirements and thus it should not be used for compounding without first verifying the quality according to USP monograph.

11. Midazolam API manufactured on 2/1/2016 was analysed and met quality standards as per BP (British Pharmacopeia) but not USP Midazolam monograph quality standards. Here is the quality report for midazolam (from 2/1/2016) as per certificate provided:

TESTS	SPECIFICATIONS	RESULTS
ASSAY ON DRIED BASIS*	98.5 - 101.5 %	99.1 %
DESCRIPTION	White or yellowish crystalline powder.	CONFORMS
IDENTIFICATION B*	IR: Reference to standard spectrum	POSITIVE
APPEARANCE OF SOLUTION*	The solution is clear and not more intensely coloured than the reference solution Y6.	CONFORMS
RELATED SUBSTANCES	≤ 0.2 % (Impurity B) ≤ 0.15 % (Impurity A) ≤ 0.15 % (Impurity E) ≤ 0.15 % (Impurity G) ≤ 0.15 % (Impurity H) ≤ 0.10 % (Unspecified impurities) ≤ 0.3 % (Total impurities)	< 0.2 % < 0.15 % 0.018 % 0.007 % < 0.15 % < 0.10 % 0.02 %
IMPURITY C	≤ 0.1 %	< 0.1 %
LOSS ON DRYING*	≤ 0.5 %	0.06 %
SULFATED ASH*	≤ 0.1 %	0.02 %
RESIDUAL SOLVENTS*	Meets the requirements.	CONFORMS
SOLUBILITY	Practically insoluble in water, freely soluble in acetone and in ethanol (96%), soluble in methanol.	
PACKAGING AND STORAGE	Preserve in tight, light-resistant containers.	
FIRST IDENTIFICATION: B	If Identification B is performed, then Identifications A, C, D, and E are not required.	

(Defts. Supp. Resp. 11.18.2021 000005).

12. Here again, the quality standards as set by British Pharmacopoeia are different from the quality requirements as set by USP, including testing methodology, and thus the quality of this product also cannot be verified and should not be used for compounding of human drugs in the US without first analysing this API using USP monograph and USP specified methodology.

13. Based on the Manual of Policies and Procedures issued by the Center for Drug Evaluation and Research, according to the guidance from the document issued by the Office of Pharmaceutical Quality titled "Acceptability of Standards from Alternative Compendia

(BP/EP/JP)” it is reasonable to accept quality standards from BP, EP, or JP only if the standards specified in those pharmacopeial compendia are equivalent or better than USP quality standards. In this case, midazolam quality standards as set by USP are not equivalent to the ones set by EP or BP. Additionally, the testing methodology and quality standards required by USP are superior to the EP and BP standards due to improved specificity. This means that the midazolam API needs to be tested using USP Monograph for midazolam.¹

14. Since the quality of the API cannot be verified using the quality reports provided, the drug may not have the potency and purity that is required for compounding of USP grade midazolam injection. This can lead to lower potency of the lethal injection chemical or other unwanted adverse effects since the impurities of the drug used have not been identified and verified. It is also critical to recognize that the compounding pharmacy did not follow USP monograph quality requirements when compounding midazolam for the Tennessee Department of Correction and the compounded midazolam injection samples when tested failed or did not meet all requirements as set by the USP monograph. (Def. 2nd Int. & RFP & RFA 000086, 000090, 000092, 000093, 000096, 000099, 000103).

II. Poor record keeping practices.

15. Generally, in pharmacy practice, appropriate record keeping is as important as the compounding activity itself. It is often said that “if it was not recorded it did not happen.” It is imperative to keep proper compounding records so they can be reviewed, ingredients can be traced when needed, for example in case of a recall, and overall quality can be verified.

16. There are a number of problems shown by the new records. First, the formula sheets presumably generated by the compounding pharmacy that compounds lethal injection chemicals for the Tennessee Department of Correction contain very limited information and

¹ European manufacturers can use USP monograph standards when testing API intended for sale to customers located in the United States. Additionally, customers located in the United States can test API purchased overseas for compliance with USP monograph standards if the API was not already tested for USP compliance by the foreign manufacturer.

demonstrate that the compounding pharmacy does not keep proper compounding records. (Defts. Supp. Resp. 11.18.2021 000015-22, 000025, 0006-38). Lot numbers for all active and inactive ingredients, their expiration dates, balance calibration records, glassware quality records, source of water for injection, pH meter (if used) and its calibration record, etc. should all be either included in this report or at least referenced. All of this information is missing.

17. Further, additional documentation should be maintained by the compounding pharmacy, such as quality reports for all excipients (inactive ingredients) used to assure that the compounding pharmacy only used pharmaceutical grade quality products that were not expired or recalled. Without quality reports (Certificates of Analysis) which are absent here, the excipients used could be laboratory or technical grade and not pharmaceutical grade. It is important not to use laboratory or technical grade reagents in compounding, even if used only in small quantities, as they are not pure and often contain harmful contaminants. There are no reports for quality of the edetate disodium, water for injection, hydrochloric acid, sodium hydroxide and benzyl alcohol, which were apparently used in compounding of midazolam for the Tennessee Department of Correction. Though some of these ingredients are listed as NF or USP grade in the compounding records, it is not certain that they truly are, because midazolam is also listed as USP grade, but the certificate of analysis does not show compliance with USP. It is critical to verify each ingredients' certificate of analysis to confirm that they all meet all compendial quality requirements and are suitable for compounding of drugs for human use.

The compounding records for potassium chloride injection appear to show that 493 mL of sterile water for injection were used to complete this preparation, as no other QS volume (Quantum Satis, or final volume to which to fill) is listed in the blank space provided on the sheet. (Defts. Supp. Resp. 11.18.2021 000020). A QS is used to indicate that a sufficient quantity of the ingredient was used to prepare a certain volume of the drug to achieve a certain percentage concentration or potency. Since 493ML is the only number listed next to sig QS, it can be

assumed that the sufficient amount of diluent was added to make 493 ML. There is no indication of the final target QS volume. If that is the case for the potassium chloride that was prepared for injection, then 17.65% solution was prepared instead of 15% solution as listed.

18. On the same record, there is an entry which is titled "New Log" and states "originally made as: 580 potassium chloride 15% injection solution concentrate injectable." There are no units listed in this entry. Again, this is extremely poor record keeping practice, as units must be listed always as mL or grams, or other appropriate unit expression. Perhaps the final volume is 580mL, however, this extremely poor recordkeeping system makes this compound questionable.

19. It is also unclear that the appropriate Beyond Use Date ("BUD") for potassium chloride was observed. Defts. Supp. Resp. 11.18.2021 000022 lists the BUD for the preparation of potassium chloride 15% as 30 days, but it is unclear what reference was used, and whether this was the BUD that was actually assigned to this preparation.

20. As the midazolam injection and potassium chloride concentrated solution are both to be used for parenteral application (injection), sterilization of the final product must be completed and should be documented. It is important to report what type of sterilization methodology was used. Most commonly, sterilization is performed by filtration of the compound using the specific filter designed for sterilization. If the filter is used, a bubble point test must be performed and documented to ensure integrity of each filter used. A bubble point test is used to verify integrity of the filter that was used to prepare the sterile product. The back pressure at which a steady stream of bubbles is produced in testing is referred to as bubble point. If the filter fails to reach expected bubble point pressure (specified by the manufacturer), the filter has failed the integrity test and the compounded product (sterilized using this filter) is not considered sterile. The documentation of this quality control measure should include the type of filter, lot number of the filter, the date of the procedure, serial number of the pressure gauge used

(to be able to trace the calibration records for the gauge), and the pressure gauge reading. The reported pressure is then compared to the pressure limit specified by the filter manufacturer to determine whether the filter remained integral during the sterilization procedure. Bubble point filter test must be performed for each high risk compound prior to dispensing.

21. Media fill testing records were also submitted for review. The first page of the log with reports starting 7/23/18 through 3/29/21 appears to be incomplete. (Defts. Supp. Resp. 11.18.2021 000023). It would also be helpful to supply the methodology used for media fill testing, as the media fill testing procedures are not standard. Instead, they must represent the most challenging conditions experienced by the compounding personnel. Non-sterile commercially available medium (as specified in USP 797) should be used to verify high-risk sterile compounding techniques used to prepare midazolam and potassium chloride compounding. Media filled vials should be incubated in 20-25 or 30-35 degrees Celsius for a minimum of 14 days. The records provided do not indicate the dates when the tests were completed and what the actual reading was. Only the second page with dates of tests performed on 9/17/21 have this information listed. But from this record it appears that QI Medical PATT 2 GroMed test kit was used, which is a test that is used for medium risk level sterile compounding media fill testing. This type of a kit should not have been used. A test kit for testing of high risk aseptic technique verification should be used in this case because high risk compounding (which compounding the lethal injection chemicals would be since non-sterile APIs are used) is always considered the most complex type of preparation, as it involves preparation of sterile preparations from non-sterile medications and involves the intricate step of sterilization that requires higher level of skills than traditional sterile to sterile compounding.

22. Inappropriate record keeping, lack of attention to detail, and poor pharmacy compounding practices lead to concerns of the overall quality of the compounded products.

III. Incorrect preparation of hydrochloric acid solution leads to concerns about overall quality of the compounded midazolam.

23. The Formula Sheet provided used for compounding of midazolam injection calls for hydrochloric acid 1% (weight to volume) that is to be used for the adjustment of pH of the midazolam injection. (Defts. Supp. Resp. 11.18.2021 000025). However, instead of 1% hydrochloric acid the pharmacy prepared 1M (1 molar) concentration which is approximately 3% solution of hydrochloric acid. (Defts. Supp. Resp. 11.18.2021 000017). The verifying pharmacist should not have released this compounded medication for use without performing further quality checks and noting that this error occurred in the compounding records.

24. According to the Formula Sheet, 5.6 mL of incorrectly prepared hydrochloric acid was used to adjust the pH of the compounded midazolam prepared for the Tennessee Department of Correction. Since no pH records or final pH of the compound is reported, it is not clear what is the pH of the final preparation. The solution may be significantly more acidic than it should be leading to pain and suffering when injected.



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